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COMPOSITIONS AND METHODS FOR THE TREATMENT OF TUMOR

Field of the Invention

The present invention relates to compositions and methods for the diagnosis and treatment of tumor.

Background of the Invention

Malignant tumors (cancers) are the second leading cause of death in the United States, after heart disease (Boring *et al.*, CA Cancel J. Clin., 43:7 [1993]).

Cancer is characterized by an increase in the number of abnormal, or neoplastic cells derived from a normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites (metastasis). In a cancerous state, a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

Alteration of gene expression is intimately related to the uncontrolled cell growth and de-differentiation which are a common feature of all cancers. The genomes of certain well studied tumors have been found to show decreased expression of recessive genes, usually referred to as tumor suppression genes, which would normally function to prevent malignant cell growth, and/or overexpression of certain dominant genes, such as oncogenes, that act to promote malignant growth. Each of these genetic changes appears to be responsible for importing some of the traits that, in aggregate, represent the full neoplastic phenotype (Hunter, Cell, 64:1129 [1991] and Bishop, Cell, 64:235-248 [1991]).

A well known mechanism of gene (*e.g.* oncogene) overexpression in cancer cells is gene amplification. This is a process where in the chromosome of the ancestral cell multiple copies of a particular gene are produced. The process involves unscheduled replication of the region of chromosome comprising the gene, followed by recombination of the replicated segments back into the chromosome (Alitalo *et al.*, Adv. Cancer Res., 47:235-281 [1986]). It is believed that the overexpression of the gene parallels gene amplification, *i.e.* is proportionate to the number of copies made.

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. For example, it has been found that the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor ($p185^{HER2}$; HER2) related to the epidermal growth factor receptor EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon *et al.*, Science, 235:177-182 [1987]; Slamon *et al.*, Science, 244:707-712 [1989]).

It has been reported that gene amplification of a proto-oncogene is an event typically involved in the more malignant forms of cancer, and could act as a predictor of clinical outcome (Schwab *et al.*, Genes Chromosomes Cancer, 1:181-193 [1990]; Alitalo *et al.*, *supra*). Thus, *erb*B2 overexpression is commonly regarded as a predictor of a poor prognosis, especially in patients with primary disease that involves axillary lymph nodes (Slamon *et al.*, [1987] and [1989], *supra*; Ravdin and Chamness, Gene, 159:19-27 [1995]; and Hynes and Stern, Biochim Biophys Acta, 1198:165-184 [1994]), and has been linked to sensitivity and/or resistance to hormone therapy and chemotherapeutic regimens, including CMF (cyclophosphamide, methotrexate, and fluoruracil) and anthracyclines (Baselga *et al.*, Oncology, 11 (3 Suppl 1):43-48 [1997]). However, despite the association of *erb*B2 overexpression with poor prognosis, the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients (*Ibid*). A recombinant humanized anti-ErbB2 (anti-HER2) monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or Herceptin™) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anticancer therapy. (Baselga *et al.*, J. Clin. Oncol., 14:737-744 [1996]).

In light of the above, there is obvious interest in identifying novel methods and compositions which are useful for diagnosing and treating tumors which are associated with gene amplification.

Summary of the Invention

The present invention concerns compositions and methods for the diagnosis and treatment of neoplastic cell growth and proliferation in mammals, including humans. The present invention is based on the identification of genes that are amplified in the genome of tumor cells. Such gene amplification is expected to be associated with the overexpression of the gene product and contribute to tumorigenesis. Accordingly, the proteins encoded by the amplified genes are believed to be useful targets for the diagnosis and/or treatment (including prevention) of certain cancers, and may act as predictors of the prognosis of tumor treatment.

In one embodiment, the present invention concerns an isolated antibody which binds to a polypeptide designated herein as PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Often, the cell that expresses the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198. In one aspect, the isolated antibody specifically binds to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. In another aspect, the antibody induces the death of a cell which expresses a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Often, the cell that expresses the PRO212, PRO290, PRO341, PRO535, PRO619,

PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is a tumor cell that overexpresses the polypeptide as compared to a normal cell of the same type. In yet another aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity determining region (CDR) residues and human framework region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In yet another aspect, the antibody is an antibody fragment, a single-chain antibody, or an anti-idiotypic antibody which binds, preferably specifically, to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide.

In another embodiment, the invention concerns a composition of matter which comprises an antibody which binds, preferably specifically, to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition of matter comprises a therapeutically effective amount of the antibody. In another aspect, the composition comprises a further active ingredient, which may, for example, be a further antibody or a cytotoxic or chemotherapeutic agent. Preferably, the composition is sterile.

In a further embodiment, the invention concerns an isolated nucleic acid molecule which encodes an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, and vectors and recombinant host cells comprising such nucleic acid molecules.

In a still further embodiment, the invention concerns a method for producing an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, wherein the method comprises culturing a host cell transformed with a nucleic acid molecule which encodes the antibody under conditions sufficient to allow expression of the antibody, and recovering the antibody from the cell culture.

The invention further concerns antagonists of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide that inhibit one or more of the functions or activities of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. Agonists of a PRO212, PRO290,

PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide are also contemplated herein.

In a further embodiment, the invention concerns an isolated nucleic acid molecule that hybridizes to the complement of a nucleic acid molecule encoding a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. The isolated nucleic acid molecule is preferably DNA, and hybridization preferably occurs under stringent hybridization and wash conditions. Such nucleic acid molecules can act as antisense molecules of the amplified genes identified herein, which, in turn, can find use in the modulation of the respective amplified genes, or as antisense primers in amplification reactions. Furthermore, such sequences can be used as part of a ribozyme and/or a triple helix sequence which, in turn, may be used in regulation of the amplified genes.

In another embodiment, the invention provides a method for determining the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a sample suspected of containing a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, wherein the method comprises exposing the sample to an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and determining binding of the antibody to a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in the sample. In another embodiment, the invention provides a method for determining the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a cell, wherein the method comprises exposing the cell to an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and determining binding of the antibody to the cell.

In yet another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising detecting the level of expression of a gene encoding a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher expression level in the test sample as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test tissue cells were obtained.

In another embodiment, the present invention concerns a method of diagnosing tumor in a mammal, comprising (a) contacting an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in said mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger quantity of complexes formed in the test sample indicates the presence of tumor in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art.

The test sample is usually obtained from an individual suspected to have neoplastic cell growth or proliferation (*e.g.* cancerous cells).

In another embodiment, the present invention concerns a cancer diagnostic kit comprising an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody and a carrier (*e.g.,* a buffer) in suitable packaging. The kit preferably contains instructions for using the antibody to detect the presence of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184,

PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in a sample suspected of containing the same.

In yet another embodiment, the invention concerns a method for inhibiting the growth of tumor cells comprising exposing tumor cells which express a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide to an effective amount of an agent which inhibits an activity and/or the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, wherein growth of the tumor cells is thereby inhibited. The agent preferably is an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, a small organic and inorganic molecule, peptide, phosphopeptide, antisense or ribozyme molecule, or a triple helix molecule. In a specific aspect, the agent, *e.g.*, the anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody, induces cell death. In a further aspect, the tumor cells are further exposed to radiation treatment and/or a cytotoxic or chemotherapeutic agent.

In a further embodiment, the invention concerns an article of manufacture, comprising:

a container;

a label on the container; and

a composition comprising an active agent contained within the container; wherein the composition is effective for inhibiting the growth of tumor cells and the label on the container indicates that the composition can be used for treating conditions characterized by overexpression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide as compared to a normal cell of the same tissue type. In particular aspects, the active agent in the composition is an agent which inhibits an activity and/or the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide. In preferred aspects, the active agent is an anti-PRO212, anti-PRO290, anti-PRO341, anti-PRO535, anti-PRO619, anti-PRO717, anti-PRO809, anti-PRO830, anti-PRO848, anti-PRO943, anti-PRO1005, anti-PRO1009, anti-PRO1025, anti-PRO1030, anti-PRO1097, anti-PRO1107, anti-PRO1111, anti-PRO1153, anti-PRO1182, anti-PRO1184, anti-

PRO1187, anti-PRO1281, anti-PRO23, anti-PRO39, anti-PRO834, anti-PRO1317, anti-PRO1710, anti-PRO2094, anti-PRO2145 or anti-PRO2198 antibody or an antisense oligonucleotide.

The invention also provides a method for identifying a compound that inhibits an activity of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide, comprising contacting a candidate compound with a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide under conditions and for a time sufficient to allow these two components to interact and determining whether an activity of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is inhibited. In a specific aspect, either the candidate compound or the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is immobilized on a solid support. In another aspect, the non-immobilized component carries a detectable label. In a preferred aspect, this method comprises the steps of (a) contacting cells and a candidate compound to be screened in the presence of PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide and (b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide in cells that express the polypeptide, wherein the method comprises contacting the cells with a candidate compound and determining whether the expression of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide is inhibited. In a preferred aspect, this method comprises the steps of (a) contacting cells and a candidate compound to be screened under conditions suitable for allowing expression of the PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005,

PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 polypeptide and (b) determining the inhibition of expression of said polypeptide.

Brief Description of the Figures

Figure 1 shows the nucleotide sequence (SEQ ID NO:1) of a cDNA containing a nucleotide sequence encoding native sequence PRO212, wherein the nucleotide sequence (SEQ ID NO:1) is a clone designated herein as DNA30942-1134. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 2 shows the amino acid sequence (SEQ ID NO:2) of a native sequence PRO212 polypeptide as derived from the coding sequence of SEQ ID NO:1.

Figures 3A through 3B show the nucleotide sequence (SEQ ID NO:6) of a cDNA containing a nucleotide sequence encoding native sequence PRO290, wherein the nucleotide sequence (SEQ ID NO:6) is a clone designated herein as DNA35680-1212. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 4 shows the amino acid sequence (SEQ ID NO:7) of a native sequence PRO290 polypeptide as derived from the coding sequence of SEQ ID NO:6.

Figure 5 shows the nucleotide sequence (SEQ ID NO:9) of a cDNA containing a nucleotide sequence encoding native sequence PRO341, wherein the nucleotide sequence (SEQ ID NO:9) is a clone designated herein as DNA26288-1239. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 6 shows the amino acid sequence (SEQ ID NO:10) of a native sequence PRO341 polypeptide as derived from the coding sequence of SEQ ID NO:9.

Figure 7 shows the nucleotide sequence (SEQ ID NO:13) of a cDNA containing a nucleotide sequence encoding native sequence PRO535, wherein the nucleotide sequence (SEQ ID NO:13) is a clone designated herein as DNA49143-1429. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 8 shows the amino acid sequence (SEQ ID NO:14) of a native sequence PRO535 polypeptide as derived from the coding sequence of SEQ ID NO:13.

Figure 9 shows the nucleotide sequence (SEQ ID NO:15) of a cDNA containing a nucleotide sequence encoding native sequence PRO619, wherein the nucleotide sequence (SEQ ID NO:15) is a clone designated herein as DNA49821-1562. Also presented in bold font and underlined are the positions of the respective start and stop codons.

Figure 10 shows the amino acid sequence (SEQ ID NO:16) of a native sequence PRO619 polypeptide as derived from the coding sequence of SEQ ID NO:15.

Figure 11 shows the nucleotide sequence (SEQ ID NO:17) of a cDNA containing a nucleotide sequence encoding native sequence PRO717, wherein the nucleotide sequence (SEQ ID NO:17) is a clone designated herein as DNA50988-1326. Also presented in bold font and underlined are the positions of the respective start and stop

Gene amplification assay:

The PRO212, PRO290, PRO341, PRO535, PRO619, PRO717, PRO809, PRO830, PRO848, PRO943, PRO1005, PRO1009, PRO1025, PRO1030, PRO1097, PRO1107, PRO1111, PRO1153, PRO1182, PRO1184, PRO1187, PRO1281, PRO23, PRO39, PRO834, PRO1317, PRO1710, PRO2094, PRO2145 or PRO2198 compounds of the invention were screened in the following primary tumors and the resulting ΔCt values are reported in Tables 3A-3D.